

2 Methodology

2.1 The developers

The National Collaborating Centre for Chronic Conditions (NCC-CC) is housed by the Royal College of Physicians (RCP) but governed by a multi-professional partners board inclusive of patient groups and NHS management. The collaboration was set up in 2000 to undertake commissions from the National Institute for Clinical Excellence (NICE), to develop clinical guidelines for the National Health Service. NICE originally commissioned the RCP and the Chartered Society of Physiotherapy (CSP) to develop this guideline. When the NCC-CC was formed, it assumed the management responsibility, but with continuing leadership from the executive leads of the CSP and RCP.

Editorial responsibility for the guideline rests solely with the development group.

Each commission is systematically developed from the current evidence base. Two multi-professional groups, supported by a technical team from the NCC-CC, were involved in the development of the guideline:

- a small **Guideline Development Group** (GDG) that met monthly and undertook the detailed evidence assessment and recommendation drafting
- an enlarged group, the **Consensus/Reference Group** (CRG), which met early in the development to ensure the clinical questions and aims were appropriate. At the end of the process, the CRG met again to review the recommendations drafted by the GDG and to consider clinically important areas where there was insufficient evidence, and where formal consensus techniques were required to develop recommendations.

Membership details can be found on page iii of this document. The groups were formed by inviting nominations from stakeholder organisations selected by the NCC-CC to ensure an appropriate mix of clinical professions and patient groups. Each nominee was expected to serve as an individual expert in their own right and not as a mandated representative, although they were encouraged to keep their parent organisation informed of the process. All group members made a formal 'declaration of interests' at the start and provided updates during the development. The NCC-CC and the group leader monitored these.

2.2 The scope of the guideline

The scope for this guideline (see Appendix J) was developed utilising the NICE stakeholder consultation process. In summary, the guideline is required to be relevant to adults of all ages with MS, and to consider the full range of care that should be routinely available from the NHS. This includes appropriate use of mainstream pharmacological, physical therapy, rehabilitation and psychosocial treatments. Existing NICE guidance relating to interferon beta and glatiramer acetate is to be incorporated into the guideline. Since this is a guideline for the NHS, it should comment on the interface with other sectors but will not consider them in detail.

2.3 Involvement of people with MS

The NCC-CC was keen to ensure that the guideline development process was informed by the views of people with MS and their carers. This was achieved in two ways:

- by securing patient organisation representation on the guideline development groups
- by carrying out focus groups and interviews to ensure that the views of people directly affected by MS informed the guideline development process.

The Multiple Sclerosis Society and the Multiple Sclerosis Trust had a representative each on the development groups. They were therefore involved at every stage of the guideline development process and were able to consult with their wider constituencies throughout the process.

Before the first meetings of the development groups, focus groups were held to identify issues that people with MS consider important when describing the impact of MS on their lives. The study had three stages:

- focus groups with people with MS (one for people with mild to moderate MS and one for people with moderate to severe MS)
- focus group with carers of people with MS (one group)
- one-to-one interviews with people with severe MS who were fully dependent.

The patient organisation representatives helped to recruit people with MS to participate in each of the groups. Trained facilitators from the NICE Patient Involvement Unit based at the College of Health ran the groups and interviews.

Further information about this study can be found in a separate document (to be issued later). A summary of the key findings from the study and how these have informed the guideline recommendations can be found in Appendix B.

2.4 Searching for the evidence

There were three stages to this process.

- 1) First, the technical team set out a series of specific clinical questions that covered the issues identified by the project scope. The CRG met to discuss, refine and approve these questions as suitable for identifying appropriate evidence within the published literature.
- 2) The information scientist then developed a search strategy to identify the evidence for each question. Identified titles and abstracts were reviewed for relevance to the agreed clinical questions and full papers obtained as appropriate. Full papers were assessed for inclusion according to predefined criteria (Appendix C).
- 3) Finally, the full papers were critically appraised and the relevant data entered into evidence tables (see Table 1) which could be reviewed and analysed by the GDG as the basis upon which to evaluate recommendations.

Limited details of the searches with regard to databases and constraints applied can be found in Appendix C. Grey literature was searched for using the System for Information on Grey Literature in Europe (SIGLE) database. Stakeholder evidence identified via the NICE process⁹ was incorporated where appropriate.

In some sections systematic searches were not undertaken because the issue under consideration was not MS specific. Non-systematically retrieved supporting information for these sections is presented.

Evidence on cost-effectiveness was extracted from the main searches wherever it existed, this was rare but was necessary to undertake a separate search for information on the potential costs and benefits of the interventions and management strategies considered in this guideline. This search was carried out by the information resources section in the School for Health and Related Research at the University of Sheffield, and was designed in collaboration with the health economist. The GDG realised that few formal cost effectiveness analyses would be identified, therefore the search for economic evidence was very broad and designed to identify information about the resources used in providing a service or intervention and/or the benefits that can be attributed to it. No study design criteria were imposed *a priori*, ie the searches were not limited to randomised controlled trials (RCTs) or formal economic evaluations. Further details of the searches for economic evidence are given in Appendix D.

Identified titles and abstracts from the economics searches were reviewed by the health economist, and full papers obtained as appropriate. The health economist critically appraised the full papers and the relevant data was conveyed to the group alongside the clinical evidence for each question. Given that the economics searches were so broad and that no standard measure of assessing the quality of economic evidence is available, careful consideration was given to each study design and the applicability of the results to the guideline context.

A further important aim of the economics searches was to identify the key gaps in evidence on potential costs and benefits; hence the titles and abstracts were mapped to the clinical questions at an early stage, so that the GDG could decide which areas to prioritise for further work (see below).

Identifying relevant literature and evidence, evaluating the strength of that evidence, and collating it into a usable form required great efforts. It has to be recognised that:

- Relevant, often important evidence is scattered very widely, often in sources that are not easily available and sometimes not indexed.
- Much of the relevant evidence is not specific to MS (for example, evidence on the management of neuropathic pain is of great relevance but few studies are exclusively based on MS). This applies to most impairments and activities.
- Much of the evidence on costs and benefits comes from the US health care system and is therefore of limited applicability to a UK guideline.
- The scope of the topic is such that there is a great volume of evidence that the GDG considered to be of very variable quality.

2.5 Synthesising the evidence

Each paper was assessed for its methodological quality against pre-defined criteria (based upon CRD report 4 for RCTs and systematic reviews (SRs)¹⁰ and the QUADAS tool for diagnostic accuracy studies¹¹ (full details are available on request)).

Papers that met the inclusion criteria were then assigned a level according to Table 1 (overleaf).¹²

The clinical question dictated the appropriate study design that should be sought and the level was then assigned as above. RCTs were the most appropriate study design for a number of clinical questions and RCTs lend themselves particularly well to research into medicines.

Table 1 Grading scheme and hierarchy of evidence*

Recommendation grade	Evidence
A	Directly based on category I evidence.
B	Directly based on category II evidence, <i>or</i> extrapolated recommendation from category I evidence.
C	Directly based on category III evidence, <i>or</i> extrapolated recommendation from category I or II evidence.
D	Directly based on category IV evidence, <i>or</i> extrapolated recommendation from category I, II or III evidence.
DS	Evidence from diagnostic studies.
HSC	Health service circular 2002/2004.
Evidence category	Source
Ia	Evidence from meta-analysis of randomised controlled trials.
Ib	Evidence from at least one randomised controlled trial.
IIa	Evidence from at least one controlled study without randomisation.
IIb	Evidence from at least one other type of quasi-experimental study.
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies.
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities.

*Adapted from Eccles M, Mason J.¹²

However, they were not the most appropriate study design for some other questions, particularly in the area of rehabilitation where interventions are often tailored to the needs of the individual. The result is that evidence on pharmaceutical interventions tended to receive higher levels than for other equally valid interventions. This should not be interpreted as a preference for a particular type of intervention nor as a reflection on the quality of the evidence for questions where non-RCT evidence is valid and appropriate.

2.6 Health economics evidence

The mapping exercise, based on the titles and abstracts identified in the broad search for economic evidence, confirmed that very little information on cost effectiveness was available; of the 464 papers identified there were only nine economic evaluations based on RCTs. In general the economic information came from studies that considered either costs or outcomes but not both. In addition the majority of studies did not investigate specific interventions or services, but rather considered the overall cost of MS to society and/or the individual with the condition, or they dealt with measuring quality of life in general in MS. This evidence could only be of limited use in informing the recommendations.

The health economics input was therefore distinguished according to whether or not formal economic evaluations were available. Where this type of evidence did exist it was presented alongside the clinical evidence with advice on the quality of the evidence and its applicability to the recommendations. However, in the majority of areas there was no formal economic evidence and this problem was exacerbated by a lack of systematic and readily available information on:

- the potential costs and benefits of any of the specific interventions or models of service delivery considered – this is particularly problematic in relation to benefits, as costs can often be estimated from other sources
- the current resource use associated with MS both in the NHS and wider society
- the current range of clinical practice within the NHS.

While health economic analysis can provide a framework for collating information from a variety of sources in order to estimate, and systematically compare, costs and benefits, this is a complex and labour intensive process and it does require a level of clinical evidence that is not readily available in MS. As a result the group prioritised those areas, which they believed would benefit most from additional information on costs and benefits. Priorities were assessed on the basis of:

- potentially large health benefits
- a potentially large effect on NHS resources (positive or negative)
- considerable uncertainty surrounding the benefits and resources
- potentially large service impact
- important equity considerations.

A number of areas were suggested by the health economist and the clinical advisor, and the GDG identified three priorities: the use of magnetic resonance imaging (MRI) scans in the diagnosis and continued management of MS; the delivery of high dose corticosteroids for acute relapse; and the issue of specialist *vs* generalist services for the provision of care. This third area was not explored in detail due to time constraints. Details of the work carried out in the first two areas are included in Appendices E and F.

2.7 Drafting the recommendations

Evidence for each topic was extracted into tables and summarized in graded evidence statements. The clinical advisor used this evidence to draft recommendations that were provided to the group prior to the meetings. The GDG reviewed the recommendations and their grading at their meetings and reached a group opinion. Recommendations were explicitly linked to the evidence that supports them and then graded according to the level of the evidence upon which they were based. Although the grade given to a recommendation reflects the level of evidence on which it is based, it does not necessarily reflect the importance attached to the recommendation. Furthermore, the level of evidence is based on a single hierarchy of research design, but in reality different designs are appropriate for different types of research problem. Specifically in research into rehabilitation and research involving people with long-term conditions, other designs and methodology such as single case studies, quasi-experimental designs, qualitative studies and correlational studies based on prospective observational cohorts will often be stronger than randomised controlled studies. Consequently many of the recommendations that received a grade D were nonetheless those that the GDG felt were the most important.

2.8 Agreeing the recommendations

A one-day meeting of the CRG was held after the evidence review had been completed and when an early draft of the guideline produced by the GDG was available. The CRG considered the draft guideline in two stages using a Rand modified nominal group technique,¹³ first via a pre-meeting vote and again in a formal meeting:

- 1) Are the evidence-based statements acceptable and is the evidence cited sufficient to justify the grading attached?
- 2) Are the recommendations derived from the evidence justified and are they sufficiently practical so that those at the clinical front line can implement them prospectively? There were three types of recommendation to be considered:
 - a) A recommendation from the GDG based on strong evidence – usually non-controversial unless there was important evidence that had been missed or misinterpreted.
 - b) A recommendation that was based on good evidence but where it was necessary to extrapolate the findings to make it useful in the NHS – the extrapolation approved by consensus.
 - c) Recommendations for which no evidence exists but which address important aspects of MS care or management – and for which a consensus on best practice could be reached.

The formal consensus methods that have been established within the NCC-CC, drawing on the knowledge set out in the health technology appraisal,¹³ and practical experience. It made full use of electronic communication and voting techniques and will be fully described in separate publications

2.9 Writing the guideline

The guideline was drawn up by the technical team in accordance with the decisions of the guideline development groups. The draft guideline was circulated to stakeholders according to the formal NICE stakeholder consultation and validation phase⁹ prior to publication, and modifications, approved by the GDG, were made as a result.